IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re application of: | Confirmation No.: 9669 |
| SETTE *et al.* | Art Unit: 1644 |
| Appl. No.: 09/357,737 | Examiner: Schwadron, R.B. |
| Filed: July 19, 1999 | Atty. Docket: 2473.0030005/PAJ/M-M |
| For: **Inducing Cellular Immune Responses to Hepatitis C Virus Using Peptide and Nucleic Acid Compositions** | |

# Declaration of Alessandro Sette, Ph.D. Under 37 C.F.R. § 1.132

***Mail Stop Amendment***

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Alessandro Sette, Ph.D. declare and state that:

1. I am Head of the Center for Infectious Disease, Allergy & Asthma Research at the La Jolla Institute for Allergy and Immunology (LIAI). Since joining LIAI in 2002, I have also held the positions of Head of the Initiative for Emerging Diseases and Biodefense and Head of the Division of Translational Immunology. My research focuses on the identification of epitopes, working to understand how vaccines should be constructed. My current work is focused on emerging disease threats or bioterror threats, such as SARS, arena viruses, smallpox and flu viruses. I have been awarded a long-term contract from the National Institute of Allergy and Infectious Disease (NIAID) to design and produce a national Immune Epitope Database (IEDB) to aide in the acceleration of vaccine development on a global scale.

2. I received my degree in Biological Sciences from the University of Roma, Laboratory of Pathology in 1984. In 1984, I became a Postdoctoral Fellow in the same laboratory. From 1986-1988, I joined The National Jewish Center for Immunology and Respiratory Medicine in Denver,

Colorado. In 2002, I was named Adjunct Professor in the Department of Experimental Medicine at the Scripps Research Institute, where I was also Scientific Director of the Rheumatic Diseases Core Center. In 2003, I was named Adjunct Professor in the Department of Medicine at the University of California, San Diego. I am a member of numerous grant review panels and a reviewer for many scientific publications. I am also a member of the editorial advisory board for the following journals: *Immunogenetics*, *Human Immunology*, *Current Pharmaceutical Biotechnology*, *Current Drugs*, and *Tissue Antigens*. I am an author on over 400 peer-reviewed publications in the fields of immunology and vaccine development.

3. My *curriculum vitae* is attached as **Exhibit A.**

4. I am an inventor of the subject matter claimed in the above-identified application.

5. I have read and understood the above-identified application and pending claims, as well as the Office Action dated March 25, 2009 ("Office Action").

6. I have been informed by attorneys for Pharmexa that the specification of a patent application describes the claimed invention while the claims establish the scope of the invention. I understand that claims 166, 168, 170, 177 and 247 are directed to an isolated peptide selected from a group that includes the peptide GVAGALVAFK, as well as conjugates and compositions comprising this peptide.

7. The GVAGALVAFK peptide harbors an A3 supermotif, characterized in the specification by the presence of an A, L, I, V, M, S, or T as a primary anchor at position 2, and a positively charged residue, R or K, at the C-terminus. (*See* Specification, page 28, lines 2-4.) A peptide harboring a

particular supermotif is often indicative of its ability to bind to several allele-specific human leukocyte antigens (HLAs).

8. It is my understanding that the claims under consideration have been rejected in the outstanding Office Action for allegedly being obvious in view of: (1) Chien *et al.*, U.S. Patent No. 6,150,087 ("Chien"); (2) Berzofsky *et al.*, U.S. Pat. No. 5,980,899 ("Berzofsky"); and (3) Guo *et al.*, *Nature 360*:364-366 (1992) ("Guo").

9. I have been informed by attorneys for Pharmexa that an invention is considered "obvious" if the differences between the subject matter sought to be patented and the prior art (for example, published applications or journal articles) are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. I have been further informed that one way to consider whether an invention is obvious is to consider whether there are a finite number of identified, predictable solutions that would lead one of ordinary skill in the art to arrive at the claimed invention.

10. In my view, a "person of ordinary skill in the art" with respect to the above-identified patent application would be a person having a high level of education, *e.g.*, a Ph.D., an M.D., or equivalent degree, and/or significant training in immunology, virology and/or vaccine development.

11. I have read and understand the references cited by the Examiner in the Office Action. As discussed further below, it is my view that a person of ordinary skill in the art, looking at Chien, Berzofsky and Guo, would not be able to predictably arrive at the claimed peptide, GVAGALVAFK.

12. Chien is essentially the disclosure of the hepatitis C virus (HCV) sequence, described as a newly discovered etiologic agent of Non-A,

Non-B hepatitis (NANBH). *See* Chien, col. 4, lines 45-49. The sequence of the HCV genome disclosed in Chien is ~3000 amino acids in length. In columns 27-28, Chien lists a series of overlapping amino acid fragments that have been arbitrarily generated and span the entire HCV genome. The AA1850-AA1900 fragment, referenced by the Examiner in the Office Action, is only 1 of the 188 fragments listed in columns 27-28. Each of these 188 fragments varies in size, from approximately 5 to 265 amino acids in length.

13. While Chien discloses the sequence of the HCV genome and suggests that antigenic polypeptides derived from this sequence can be prepared, Chien does not specify that any one of the 188 fragments described above would serve as a better starting point than another. Looking at Chien, each of the 188 fragments would be an equally reasonable alternative with which to start in the process of selecting an antigenic peptide.

14. A researcher in the field of immunology or vaccine development whose goal was to find an HCV peptide capable of eliciting an immune response at the time the claimed invention was made would likely consider the entire ~3000 amino acid sequence of the HCV genome disclosed in Chien.

15. Beyond arbitrarily generating polypeptide fragments of diverse and varying lengths that span across the entire HCV sequence, and screening and testing these fragments, Chien offers no further suggestion as to how to narrow down the thousands of possible peptides that could be generated by this brute force method to arrive at one, or even a reasonable number, of possible immunogenic peptides.

16. Certainly, Chien does not point to the specific GVAGALVAFK peptide as claimed, which is embedded in one of the 188 fragments of the ~3000 amino acid length sequence of HCV.

17. Therefore, it is my opinion that Chien does not provide a sufficiently finite number of identifiable, predictable solutions that would allow one of ordinary skill in the art to select the claimed peptide.

18. It is further my opinion that the guidance in Berzofsky does not help to narrow down the vast number of reasonable alternatives of Chien. Thus, it is my view that the combination of the Berzofsky and Chien references also does not offer a finite number of identifiable, predictable solutions such that one of ordinary skill in the art could arrive at the claimed peptide.

19. Berzofsky only provides the generic guidance that "there is a need to identify an epitope of HCV that is recognized by T cells." (Col. 2, lines 39-40.)

20. The presently claimed peptide is an NS4 (non-structural protein 4) peptide. Berzofsky provides no guidance to look for a peptide in the NS4 region, and in fact, indicates the lack of functional information regarding this region. In particular, Berzofsky states that "[t]he non-structural proteins are named NS1 through NS5, but the functions of only NS3 and NS5 have been assigned with certainty. NS3 is the viral protease and probably a helicase. NS5 is the viral RNA-dependent RNA polymerase." (Col. 1, lines 34-38.)

21. Berzofsky provides only very generic guidance to identify an HCV peptide epitope. In my opinion, Berzofsky does not direct a researcher in the field to narrow down their potential search for epitopes to the one particular region of HCV (NS4) in which the claimed peptide is located. In fact, the primary focus of the Berzofsky study is to examine the role of 28 CTL epitopes derived from the HCV NS5 protein. (*See* Col. 5, lines 23-38.)

22. With respect to the Guo reference, the Examiner has stated that Guo teaches that CTL recognize viral peptides complexed with MHC and that peptides which bind HLA-Aw68 generally are 9 to 11 amino acids with a V at P2 and a K at the C-terminal position. (*See* Office Action, page 4.)

23. In making this statement, the Examiner has arbitrarily focused on only one of the potential HLA-Aw68 peptide motifs disclosed in the publication. Guo discloses more than this one motif. Guo also teaches that HLA-Aw68 peptides are characterized by a V at P2 and an R at the C-terminus; and a T at P2 and an R at the C-terminus. (*See* Guo, page 364, Table 1.)

24. Considering all of the motifs in Guo, and considering the entire ~3000 amino acid sequence of Chien, one of ordinary skill in the art would generate nearly 60 possible peptides looking at these references in combination. From these nearly 60 possible peptides, one of ordinary skill in the art would have no further guidance from Chien, Berzofsky, or Guo to narrow down the possibilities to a fewer number of peptides, and certainly would have no information to select the claimed peptide.

25. The number of nearly 60 possible peptides, however, is a number of possible options when considering the motif disclosed in Guo only. Other motifs were known in the art.

26. The Examiner states that "[i]t is also noted that there are only a small number of peptides encompassed by the motif taught by Guo et al." (Office Action, page 4.) In my opinion, this statement is misleading as Guo is only one of numerous publications disclosing a subset of motifs that are characteristic of a subgroup of CTL-inducing peptides that bind to certain HLA alleles.

27. In my opinion, looking only at Guo for guidance with respect to identifying a particular CTL-inducing peptide, is not an appropriate analysis. Numerous additional motifs were disclosed and taught in the prior art at the time filing of the present invention.

28. In my view, a researcher in the field at the time of filing of the present invention would have been as interested in identifying an immunogenic peptide having, for example, an A2 motif, as he or she would have had in identifying an immunogenic peptide having an A3 motif. Similarly, a researcher in the field would also have been interested in identifying an immunogenic peptide having one of any number of motifs, each of which would have been an equally reasonable alternative.

29. The Examiner states that "a routineer would have identified such peptides as potentially pertinent to the antiHCV response in HLA-Aw68 positive patients." (Office Action, page 5.) The Examiner, however, disregards the point that a "routineer," or a person of ordinary skill in the art, would have been equally interested in identifying peptides pertinent to an anti-HCV response in patients positive for numerous other individual HLA alleles. In fact, a researcher in the field would likely be interested in identifying a peptide for inclusion in an HCV vaccine that would have broad population coverage. At a minimum, therefore, a researcher would consider numerous other motifs to be as equally relevant as the HLA-Aw68 motif.

30. In fact, the HLA-Aw68 motif disclosed in Guo occurs relatively infrequently in the population as compared to, for example, A3 and A11. The HLA-Aw68 motif would not necessarily be a motif that one of ordinary skill in the art would look at to identify an HCV peptide that would stimulate an immune response across a broad spectrum of the population.

31. Indeed, numerous other motifs were known in the art at the time of filing the present invention. For example, Jardetzky *et al.*, *Nature* 353: 326-327 (September 1991) (Exhibit B) discloses an HLA-B27 motif where the peptides that bind to HLA-B27 are usually nonamers containing an R at P2, a positively charged amino acid at P1/P9, a hydrophobic amino acid at P3 and a nonpolar or small polar amino acid residue at P6. (*See* page 327, second column through page 328, first column.)

32. In addition, Hunt *et al.*, *Science 255*:1261-1263 (March 1992) (Exhibit C) discloses an HLA-A2.1 motif where peptides that bind to HLA-A2.1 are generally nine amino acids in length and have an L or I at P2 and an amino acid residue with an aliphatic side chain at P9. (*See* page 1262 column 3 through page 1263, column 1.)

33. As an additional example, Falk *et al.*, *Immunogenetics 38*: 161-162 (February 1993) (Exhibit D) describes peptide motifs of HLA-B35 and -B37, where HLA-B35 motif is preferentially P, A, V at P2, K, D, E at P4, Y, E, M, L, I at P9 and B-37 motif is preferentially D, E at P2, V, I at P5, F, M, L at P8 and I, L at P9. (*See* Table 1, page 162.)

34. It is my view that a researcher attempting to identify an epitope of HCV that is recognized by T cells would have considered all known motifs, such as those as disclosed in, for example, Jardetzky, Hunt and Falk, and not just the several motifs disclosed in Guo.

35. Applying the additional motifs as disclosed, for example, in Jardetzky, Hunt and Falk, in view of the entire HCV genome sequence, would result in hundreds or even thousands of CTL peptide candidates. Even applying Guo alone would result in nearly 60 possible CTL peptide candidates.

36. Therefore, in view of the discussion above, it is my opinion that one of ordinary skill in the art, considering the art related to CTL peptide motifs

as a whole, would not be able to narrow down the huge number of equally reasonable HCV CTL epitope candidates to a more finite number of identifiable, predictable options.

37. Furthermore, the identification of potential candidate epitopes based on motif is only a first step. In comparison to the cited art, the present application considers several factors other than the nature of the crucial anchor residues to identify specific HCV peptide epitopes. Examples of subsequent steps include: (1) determination of binding affinity of a potential peptide epitope; (2) cross-reactivity of potential peptide epitopes to two or more allele-specific HLA molecules; (3) conservancy among various diverse HCV isolates; and (4) determination of immunogenicity, such as demonstration of sequence-specific recall responses with subsequent challenge. Each of these subsequent steps serve to select the most promising epitopes useful for inclusion into a vaccine. (*See* Specification, Example 10, pages 79-81.)

38. The sequence and/or motif of a peptide does not allow one to be able to predict whether a specific peptide would have desired characteristics according to the factors listed above. Thus, even given a finite number of identifiable peptides, one of ordinary skill in the art may still not arrive at a CTL-inducing peptide with the desired characteristics. Certainly, in the present situation, where the prior art does not provide a finite number of identifiable, predictable peptides, the factors described above would only result in additional variability and unpredictability.

39. Therefore, it is my opinion, using Chien, Berzofsky and Guo as guidance, a person of ordinary skill in the art, at the time of filing of the present invention, would not have predictably arrived at the peptide as claimed.

40. In the present application, and distinct from the cited art, my co-inventors and I identified that the claimed peptide GVAGALVAFK exhibits the

highest level of CTL-inducing response in transgenic mice in comparison to other selected peptide candidates listed in Table XXIII. In addition, as shown in Table XVI, the GVAGALVAFK peptide exhibits one of the strongest binding affinities as compared to over 400 other peptides which share the same A3 motif. These characteristics could not have been predicted from motif alone. In fact, other peptides listed in Table XXIII that share the same A3 motif as the GVAGALVAFK peptide do not exhibit as great of a response in transgenic mice.

41. Thus, the CTL-inducing and binding characteristics of the GVAGALVAFK peptide, as identified in the present application, demonstrates that the GVAGALVAFK peptide is a preferred immunogenic HCV peptide.

42. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief obtained from the references and documents discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Title 18 United States Code Section 1001, and that willful false statements may jeopardize the validity of this application or any patent issuing thereon.

43. I have read, I am familiar with, and I understand, the provisions of 37 C.F.R.§§ 10.18(b) and (c) relating to the effect of signature and certificate for correspondence filed in the U.S. Patent and Trademark Office.

Date: September 18, 2003

Alessandro Sette, Ph.D.